Report on the

Global Immunization Division Research Program, 2011–2013

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Front and back cover photos of a 2013 measles and rubella campaign in Cambodia by Susan Y. Chu.

Graphic design by Kate Mollenkamp, MS (Northrop Grumman/CDC, Atlanta).

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Abbreviations and Acronyms

AFP	acute flaccid paralysis
bOPV	bivalent oral polio vaccine
CDC	Centers for Disease Control and Prevention
CRS	congenital rubella syndrome
DBS	dried blood spots
DFWED	Division of Foodborne, Waterborne, and Environmental Diseases
DOV	Decade of Vaccines
DRC	Democratic Republic of the Congo
DVD	Division of Viral Diseases
fIPV	fractional inactivated polio vaccine
GAP	Global AIDS Program
GAVI	Global Alliance for Vaccines and Immunizations
GID	Global Immunization Division
GVAP	Global Vaccine Action Plan
HBsAG	hepatitis B surface antigen
IPV	inactivated polio vaccine
MBA	multiplex bead assay
MOH	Ministry of Health
MR	measles-rubella
OFS	oral fluid samples
OPV	oral polio vaccine
PRNT	plaque reduction neutralization test
RCV	rubella-containing vaccine
SAGE	Strategic Advisory Group of Experts
SALT	Stimulate, Appreciate, Listen/Learn, and Transfer
SBAs	skilled birth attendants
SIAs	supplementary immunization activities
SMS	short message services
tOPV	trivalent oral polio vaccine
UNICEF	United Nations Children's Fund
VAPP	vaccine-associated paralytic polio
VHV	village health volunteers
VPDEEB	Vaccine Preventable Disease Eradication and Elimination Branch
WHO	World Health Organization

Introduction

Beginning in FY 2011, the Vaccine Preventable Disease Eradication and Elimination Branch (VPDEEB), Global Immunization Division (GID), Centers for Disease Control and Prevention (CDC), established a competitive "request for proposal" mechanism to support polio, measles, rubella, and hepatitis B vaccine research projects that address elimination or eradication issues. The main goals of this branch initiative include building a stronger research program in VPDEEB and establishing new or strengthening current collaborations with international research partners. Each year, VPDEEB scientists submit proposals for potential projects, which are ranked and selected for funding based on the following criteria:

- High public health impact
- Clear goals and objectives
- Strong scientific methods
- Realistic plan of action and timeline
- Reasonable proposed budget

Total funding varies annually based on available resources. This report provides a summary of accomplishments from the first 3 years of this research initiative in context of the Global Vaccine Action Plan (GVAP). Approved by the World Health Assembly in May 2012, the GVAP is a framework to prevent millions of deaths and achieve the Decade of Vaccines' (DOV) vision of providing universal access to immunization by 2020 and beyond. The plan includes six strategic objectives toward achievement of the DOV goals. The sixth objective directly addresses "country, regional, and global research and development innovations that maximize the benefits of immunization."

Research supported by this VPDEEB/GID initiative includes human clinical trials, laboratory studies, vaccine delivery methods testing, innovative surveillance tool evaluations, and economic analyses and have involved numerous partners, including the World Health Organization (WHO), ministries of health, nongovernmental organizations, and academic institutions.

The *Figure* shows a summary of the GVAP recommended actions for Strategic Objective 6. Numerical annotation has been added.

Research Projects Funded During 2011–2013

This report provides links to the Global Vaccine Action Plan recommended action(s) and a listing of the countries and partnerships involved in research projects.

Clinical Trials and Epidemiologic Studies

A member of the survey team asks a mother in rural Laos if her child has been vaccinated for hepatitis B birth dose. Photo by Minal Patel (CDC, Atlanta).

✤ Diarrhea and Bivalent Oral Polio Vaccine Response Trial, Nepal

Objective and impact: To determine whether infants underimmunized for polio 6 weeks to 12 months of age with diarrhea are less likely to seroconvert after a dose of bivalent oral polio vaccine (bOPV) compared with underimmunized infants without diarrhea. This is the only such trial worldwide that will assess potential interference with seroconversion to bOPV; results will help guide the Global Polio Endgame Strategy.

Polio campaign, Nepal. Photo by Adam Bjork (CDC, Atlanta).

Status and outcomes: Data have been collected and specimens are currently being analyzed in the CDC laboratory. A published manuscript is expected by 2015.

GVAP linked actions: Ic; Id; IId; IVc.

✤ Comparison of Sequential Schedules of Fractional Inactivated Polio Vaccine, Bangladesh

Objective and impact: This trial will assess whether a sequential schedule of fractional inactivated polio vaccine (fIPV) and bOPV results in seroconversion rates to polio types 1 and 3 comparable to routine schedules of bOPV or trivalent oral polio vaccine (tOPV). Use of fIPV given intra-dermally has been shown to result in suboptimal immunogenicity compared with full dose IPV given intramuscularly. A sequential schedule of fIPV and bOPV could provide a cost-effective polio endgame strategy that will maintain type 2 poliovirus immunity and potentially result in better immunogenicity than tOPV, especially for type 3 poliovirus.

Status and outcomes: The trial is completed and results will be presented to the WHO Polio Research Committee meeting in May 2014; a manuscript with final results is being prepared.

GVAP linked actions: Ic; Id; IIb; IId.

✤ Timing of the First Dose of Measles Vaccine, China

Objective and impact: To determine the loss of maternal antibodies in infants 1–7 months of age born to mothers with vaccine and natural infection induced immunity and to assess seroconversion rates in these infants after measles vaccination at 8 months of age. China is nearing the elimination of indigenous measles transmission after implementing several successful vaccination strategies that have resulted in an increasing proportion of cases occurring in infants too young for vaccination. These findings will help determine whether the current recommended age of 8 months for the first dose of measles vaccine is the optimal time given current measles epidemiology in China.

Status and outcomes: Enrollment began in early 2014.

GVAP linked actions: Ia; Id; IIb; IId.

✤ Susceptibility of Polio, Measles, and Rubella Among Pregnant Women, 2008–2010, Namibia

Objective and impact: To determine age-specific immunity levels for polio, measles, and rubella among pregnant women in Namibia and to determine their association with HIV status. Namibia experienced a polio outbreak in 2006 and a large measles outbreak during 2009–2010, and in both outbreaks, adults were disproportionately affected. Namibia is also considering introducing rubella vaccine into the routine immunization schedule. This study will evaluate the role adults play in sustaining outbreaks in an African country with high HIV seroprevalence, a possible host factor affecting seroconversion and sustained immunity. It will also assist with estimation of congenital rubella syndrome (CRS) cases and rubella vaccine introduction timing.

Status and outcomes: The polio portion of the study is completed and the manuscript presenting the findings is in press (Cardemil C, Jonas A, Gerber S, Weldon W, Oberste MS, Beukes A, Sawadogo S, et al. Polio immunity among pregnant women aged 15–44 years, Namibia, 2010. J Infect Dis). The measles and rubella tests are pending.

GVAP linked actions: Ic; IIe.

✤ Maternal, Fetal, and Neonatal Outcomes Associated with Measles During Pregnancy: Namibia, 2009–2010

Objective and impact: To describe clinical complications associated with measles during pregnancy in a resource-limited setting. This retrospective cohort study found that, compared with pregnant women without measles, pregnant women with measles had significantly higher risks for low birth weight, spontaneous abortion, and maternal mortality. Increasingly, measles outbreaks are affecting adults, especially in settings with persistent suboptimal measles vaccination coverage; this study provides impetus for ensuring measles immunity among women of childbearing age, especially in areas with continuing measles transmission.

James Goodson (front), CDC epidemiologist and measles expert with the Namibia clinical manager. These tents were set up as measles isolation wards for hospitalized measles patients at the Opuwo District Hospital in Namibia during the nationwide outbreak in 2009-2010.

Status and outcomes: The project is complete and results have been published. Ogbuanu IU, Zeko S, Chu SY, Muroua C, Gerber S, de Wee L, Kretsinger K, Wannemuehler K, Allies T, Sandhu H, Goodson JL. Maternal, Fetal, and Neonatal Outcomes Associated with Measles During Pregnancy: Namibia, 2009–2010. Clin Infect Dis 2014; 58(8): 1086–1092.

GVAP linked actions: Ia; Ic; IIb.

✤ Immunogenicity of Different Oral Polio Vaccines Administered at 2-Week Versus 4-Week Intervals, Bangladesh

Objective and impact: To compare the immunogenicity of oral polio vaccines using a 2-week interval versus a 4-week interval. The current recommended interval between doses of oral polio vaccines is 4 to 6 weeks. This trial will assess whether shortening the interval between immunization campaigns can achieve high population immunity more quickly and limit the size of an outbreak; both are objectives of polio endgame strategies.

Status and outcomes: Preliminary findings have been presented to the World Health Organization (WHO) and national regulatory authorities in support of a label change for bOPV use in routine immunization. A manuscript is being prepared for publication.

GVAP linked actions: Ic; Id; IIc; IId.

Scientists processing blood samples for a study on the immunogenicity of polio vaccines, Bangladesh 2012. Photo by Concepcion Estivariz (CDC, Atlanta).

✤ Risk Factors for Measles Deaths During a Large-scale Outbreak, Bulgaria

Objective and impact: To identify risk factors associated with a high number of measles deaths during an outbreak in a middle- to high-income European country. During 2009-2010, Bulgaria experienced a large measles outbreak with approximately 24,000 cases, which affected large numbers of Roma persons; 24 deaths were reported - the highest number of measles deaths reported by a European country from a single outbreak since 2002. The findings emphasized the severity of measles disease and helped increase demand for measles vaccination in a region where the potential dangers of measles may be underappreciated.

Status and outcomes: The analysis is complete, the results have been presented to the Bulgaria Ministry of Health (MOH), and a final report is being prepared.

GVAP linked actions: Ia; Id.

A young Roma girl. Photo by Laura Zimmerman (CDC, Atlanta).

- **Estimating Population Immunity to Polio, Measles, and Rubella, Myanmar and Nepal**

  Objective and impact: To estimate population immunity to polio, measles, and rubella using already collected serum samples collected from blood banks, antenatal clinics, pediatric clinics, and hospitals and compare those estimates to those obtained with a cluster serosurvey of a representative sample. Population-based serosurveys are labor-intensive, complicated to conduct, and costly. This study will assess the utility of using previously collected sera from convenience samples in a developing country setting.

  Status and outcome: Field work has been completed and preliminary results have been presented to the Nepal MOH. Data analyses are continuing and a field report and manuscript will be completed in summer 2014.

  GVAP linked actions: Ic; IIe.

- **Defining the Role of Adult Susceptibility and Internal Migration in Measles Persistence, China**

  Objective and impact: To document changes in measles epidemiology after large-scale measles supplementary immunization activities (SIAs) and identify risk factors, including internal migration patterns, on measles transmission in adults in China. The incidence of measles among adults in China has been increasing; in 2009, Beijing reported that 50% of measles cases were among adults. These findings demonstrated that, despite high measles vaccination coverage among children, existing immunity gaps in the adolescent/young adult population were enough to sustain measles transmission and present a barrier to measles elimination goals in China.

  Status and outcomes: Data collection is complete. Three manuscripts for publication are being drafted.

  GVAP linked actions: Id; IIb; IId.

- **Immunogenicity of a Routine Schedule of Fractional Inactivated Polio Vaccine or Full Dose Inactivated Polio Vaccine Administered Sequentially with Bivalent Oral Polio Vaccine, Bangladesh**

  Objective and impact: To compare seroconversion rates with different sequential schedules using one dose of fIPV or IPV with bOPV administration at 6, 10, and 14 weeks. The Global Polio Eradication Initiative has recommended the use of one dose of IPV or fIPV in routine immunization as an essential component for the switch from trivalent to bivalent OPV; this randomized trial will provide necessary data for the licensing and use of these vaccines for the impending tOPV-bOPV switch.

  Status and outcomes: Enrollment will begin in June 2014.

  GVAP linked actions: Ic; Id; IIb; IId.

Operational and Behavioral Research Studies

Mary Alleman, epidemiologist with the Global Immunization Division, CDC-Atlanta (far right) and Vololomanitra Belalahy (far left), health communications specialist with the United Nations Children's Fund-Democratic Republic of the Congo (UNICEF-DRC) discuss implementation of an innovative communication strategy to increase vaccination acceptance with project facilitators and health staff in Kadima health area, Kabalo district, Katanga province, DRC in February 2013.

✤ Establishing Immunization Services and Surveillance for Nomadic Populations, Northern Nigeria

Objective and impact: To establish and implement innovative strategies to identify, reach, and immunize nomadic populations in northern Nigeria. The Fulani, a large ethnic group in northern Nigeria, is a highly mobile population that is chronically under-vaccinated and a potential source of continuing polio virus transmission. This project will collaborate with the Nigerian National Primary Health Care Development Agency to determine migrant population movements and likely areas of congregation (e.g., veterinarian stations for livestock vaccination, border crossings) to develop coordinated outreach strategies to track, increase awareness and acceptance of vaccination, and plan for special SIAs for this high-risk population.

Status and outcome: A landscape analysis of the general migratory patterns of Fulani and other nomadic pastoral ethnic groups was presented to the Nigeria Expert Review Committee. Results were used to revise immunization guidelines, microplanning strategies practices, and inform the development of best practices.

GVAP linked actions: Ia; Ic; IIe.

✤ Improving Timely Birth Dose Hepatitis B Vaccination Through the Use of Cell Phone Technology, Laos

Objective and impact: To evaluate whether providing cell phones to village health volunteers (VHV) improves communication between the VHV and skilled birth attendants (SBAs) at health centers about imminent births so as to increase timely hepatitis B vaccination birth dose delivery and improve neonatal outcomes. About one in 12 Laotian women are chronic carriers of hepatitis B and capable of transmitting the virus to an unimmunized newborn; however, Laos national hepatitis B vaccination coverage is low. VHVs are present in more than 90% of Laotian villages; provision of cell phones will enable VHV notification of SBAs of imminent births to improve SBA attendance at home births, birth dose delivery, and the provision of other preventive health care (e.g., clean deliveries to prevent neonatal tetanus).

Distribution of cell phones to intervention districts during hepatitis B birth dose training session in Xienghone, Laos. Photo by Edna K. Moturi (CDC, Atlanta).

Status and outcomes: The study began in February 2014.

GVAP linked actions: Ia; Ic; IIa; IIe.

✤ **Using the SALT Approach to Increase Acceptance of Polio Vaccination Among Religious Communities in Katanga Province, Democratic Republic of Congo**

Objective and impact: To increase vaccination acceptance among certain religious groups in Katanga Province in the Democratic Republic of the Congo (DRC) with a long history of vaccination refusal using an innovative community communication strategy (SALT – Stimulate, Appreciate, Listen/Learn, and Transfer) that is documented by the Joint UN Programme on HIV/AIDS as a best practice. The goal of this project, supported by UNICEF-DRC, CDC, and a Congolese non-governmental organization, RDC Compétence (the implementing organization), is to change acceptance of polio vaccination leading to higher population immunity and sustained interruption of polio virus circulation.

Vololomanitra Belalahy, of UNICEF-DRC, discusses the results of a community auto-evaluation, conducted as part of the SALT Approach in Pontien community, with SALT facilitators and community volunteers, 2013. Photo by Mary Alleman (CDC, Atlanta).

Status and outcomes: Implementation began in mid–2012, and at the end of 2013, a group of independent social scientists from universities in DRC and Belgium reviewed the project as part of a larger review of all social mobilization projects that took place in Katanga Province during the same 18-month period. Evaluators concluded that the SALT Approach was appropriate for the objective of changing attitudes and behaviors toward vaccination acceptance but also concluded that a longer time frame could assure that changes would be adopted long-term and that the new attitudes would transfer to nearby communities not directly engaged in the project. The reviewers recommended future implementation for 5 years.

GVAP linked actions: Ia; Ic; Id; IIIf.

✤ **Assessment of Attitudes, Concerns, and Information Sources of Parents to Polio and Measles Vaccination, China**

Objective and impact: To assess current attitudes of Chinese parents about polio and measles vaccination using qualitative mixed-methods research (e.g., focus groups, key informant interviews, media content analyses). Recently, parental concern has increased in China over the safety and necessity of childhood vaccines with high profile media stories of adverse events caused by vaccination. This project will provide a current and accurate assessment of vaccine attitudes and concerns of the Chinese public, which will inform interventions and messages to keep vaccine demand high in this highly populated nation.

Status and outcomes: The study is completed and the findings have been used by the Chinese MOH to revise adverse event reporting practices. A manuscript is being prepared for publication.

GVAP linked actions: Ia; Ib; Id; IIa; IIb.

✤ Development and Introduction of a Vaccine Communications Toolkit, European Region

Objective and impact: To develop a toolkit on health communications techniques, such as social marketing, to generate demand for vaccines. Many countries in the European Region have documented population pockets with low immunization coverage, which have resulted in a number of large outbreaks and threaten the region's goal for measles and rubella elimination by 2015. The toolkit will help frame strategies to reach these susceptible populations and improve vaccination coverage.

Status and outcomes: The toolkit has been developed and piloted in Bulgaria and Somali and will be used in 2015 in Romania, the United Kingdom (UK), and France. Preliminary results have been presented to several decision-making groups, including the Strategic Advisory Group of Experts (SAGE) Vaccine Hesitancy working group and the ministries of health of Bulgaria, Romania, Sweden, the UK, and France. The work, *The Guide to Tailoring Immunization Programmes,* is posted on the WHO European website (http://www.euro.who.int/__data/assets/pdf_file/00 3/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf).

GVAP linked actions: Ia; Ib; Id; IIa; IIb.

✤ Assessing the Impact of Hepatitis B Vaccination in Tajikistan

Objective and impact: To assess the impact of the introduction of hepatitis B vaccine in 2003 on the prevalence of chronic hepatitis B virus infection. Residual samples from persons aged 1–24 years that were collected in 2010 for a polio-related nationwide population-based serosurvey were tested for anti-HBc antigen antibodies and HBs antigen. The study found dramatically lower prevalence for both markers in vaccinated birth cohorts with >80% coverage with three doses of hepatitis B vaccine compared with unvaccinated birth cohorts. This demonstrated a substantial reduction in the prevalence of chronic hepatitis B virus infection in Tajikistan after hepatitis B vaccine introduction in Tajikistan.

Status and outcomes: Laboratory testing and data analysis have been completed, and the results have been presented to the, WHO Tajikistan Country Office and GID. A manuscript is being prepared.

GVAP linked actions: Ia; Ic; IIb.

✤ A Simplified System for Congenital Rubella Syndrome Surveillance In Resource-limited Settings, Sudan

Objective and impact: To establish and evaluate a CRS surveillance system based on conditions indicative of CRS disability in infants (e.g., cataracts, congenital heart disease, hearing impairment). In 2011, the Global Alliance for Vaccines and Immunization (GAVI) decided to support rubella vaccination introduction in eligible countries. This study will evaluate the practicality of a cost-effective and simplified CRS surveillance system in a resource-limited setting, which will provide information for vaccination policy decisions and for documenting the impact of rubella vaccine introduction.

Status and outcomes: The study will begin in 2014.

GVAP linked actions: Ib; Id; IIe.

- **Implications of Vaccine Wastage and Vial Policies and on Missed Opportunities for Measles Vaccination, East Java Province, Indonesia**

  Objective and impact: To describe and quantify current measles vaccine vial practices that may create missed opportunities for vaccination and determine the role of measles vaccine wastage policies on coverage. Measles vaccine requires cold chain, is reconstituted with diluent, and must be discarded 6 hours after reconstitution. Information from this study could be used to change practice and policy and improve measles vaccination coverage.

  Status and outcomes: The results were used by Indonesia MOHs to write a decree on missed opportunities that include revised standard operating procedures and will be sent to all districts, municipalities, and hospitals that conduct immunization programs. A manuscript for publication is in preparation.

  GVAP linked actions: Ia; Ic; Id; IIb.

- **Implementation and Evaluation of an Electronic, Community-based Disease Surveillance System in Nepal**

  Objective and impact: To expand the current passive surveillance system for acute flaccid paralysis (AFP) and measles with an innovative use of short message service (SMS). A major challenge for complete and accurate disease reporting is the inability to reach geographically dispersed or difficult to access populations. Personal cell phones are used widely in Nepal and this project will evaluate whether the use of SMS by disease surveillance notification officers will improve AFP and measles reporting in a developing country setting.

  Status and outcomes: The study is complete and a report is being prepared. To date, the system is reportedly being used by more than 70% of disease surveillance officers to report weekly AFP and measles data.

  GVAP linked actions: Ic; IIa; IIe.

- **Suspected Vaccine-associated Paralytic Polio Cases in Tajikistan**

  Objective and impact: To determine whether suspected vaccine-associated paralytic polio (VAPP) cases reported during a large polio outbreak in Tajikistan in 2010 were true VAPP cases. The suspected VAPP cases raised concerns, which could erode public confidence in polio vaccination campaigns. A review of clinical, laboratory, and immunization data was conducted, with additional testing of specimens using lineage-specific polymerase chain reaction not included in standard WHO recommended testing algorithms. Only one case met the criteria for VAPP, and at least four turned out to be co-infections of vaccine viruses with homotypic wild type polioviruses (both type 1); the results alleviated concerns about potential VAPP cases associated with mass immunization campaigns in Tajikistan.

  Status and outcomes: Case review, laboratory testing and analysis have been completed; the results have been presented to the MOH of Tajikistan, WHO Tajikistan Country Office, and WHO/EURO office.

  GVAP linked actions: Ic; IIe.

Laboratory Studies

November 2013: Kathmandu, Nepal. A study team member is collecting an oral fluid (crevicular fluid) sample by rubbing a sterile sponge along the boy's gum line for 2 minutes as his colleague monitors the time. Photo by Umid Sharapov (CDC, Atlanta).

- **Use of a Novel Multiplex Bead Assay for Integrated Serological Surveys, Cambodia and Tajikistan**

  Objective and impact: To compare the performance of the multiplex bead assay (MBA) for measuring immunity levels with standard assays for multiple antigens. Serological surveys provide information for monitoring progress towards elimination or eradication of vaccine-preventable diseases. The MBA has several advantages over traditional serological tests, including the ability to test for multiple antigens simultaneously with very small amounts of blood, potentially a more efficient and cost-effective assay for monitoring progress in multiple disease elimination and reduction initiatives.

  Status and outcomes: Sera collected from a nationally representative sample of women 15–39 years old in Cambodia have been analyzed and two manuscripts are being prepared for publication. Evaluations of the MBA are planned for hepatitis and rubella serology using samples from Cambodia and Tajikistan.

  GVAP linked actions: Ic; IIb; IIe.

- **Development and Validation of a Novel Neutralization Test for Measles**

  Objective and impact: To develop a highly sensitive and efficient serologic test to replace the time-consuming and complicated plaque reduction neutralization test (PRNT) for measuring measles antibodies. Measles seroprevalence studies are increasingly being conducted to estimate population level measles immunity; development of a test amenable to automation could provide faster and more cost-effective results compared with the current gold standard PRNT.

  Status and outcomes: Preliminary results from animal model tests were presented at the Global Measles and Rubella Management Meeting in WHO Headquarters, Geneva; further testing is continuing.

  GVAP linked actions: Ic; IIb; IIe.

- **Increased Immunogenicity to Inactivated Polio Vaccine with Controlled Antigen Delivery with Microneedles**

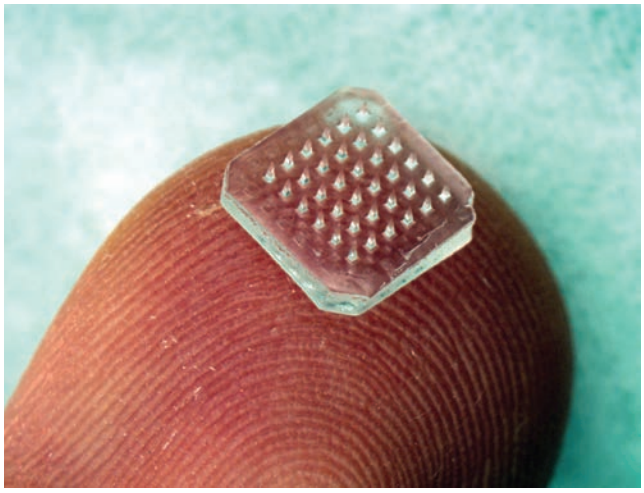
  Objective and impact: To identify a release profile that optimizes immune responses with microneedle delivery of IPV. The slow release of vaccine using microneedles more closely mimics natural infection, which may elicit a stronger immune response compared with a bolus injection of IPV. This study will determine the effectiveness of various time and dose combinations of IPV using injection versus microneedle delivery. These findings could result in a dose sparing strategy that improves the affordability of IPV, enabling polio eradication efforts.

  Status and outcomes: Preliminary results have been presented at a technical conference in July 2013. A manuscript is being prepared for publication.

  GVAP linked actions: IId; IIIb.

✤ Microneedle Patches for Polio, Measles, and Rubella Vaccination in a Nonhuman Primate Model

Objective and impact: To compare the immunogenicity of polio, measles, and measles-rubella (MR) vaccines using microneedles with subcutaneous injection. Most vaccines, including IPV, measles, and MR vaccines, are given by hypodermic injection. Microneedle patches, which are micron-scaled solid needles coated with a dry formulation of vaccine that penetrate and rapidly dissolve into skin upon application, have significant advantages over injection delivery. Microneedles cause little to no pain, require minimal training of health personnel for administration, reduce transportation and storage needs, and eliminate needle-and-syringe disposal and potential re-use. Microneedle patch vaccination could have a tremendous impact on the cost and coverage of vaccines and be a potential game-changer for efforts to achieve polio, measles, and rubella eradication and elimination goals.



A patch containing 36 dissolving microneedles is shown on a fingertip. The microneedles dissolve within minutes after insertion into skin to release vaccine. Each microneedle is 900 micrometers tall. Photo by Jeong-Woo Lee (Georgia Tech).

Status and outcomes: Seroconversion tests in rhesus monkeys with microneedles and subcutaneous injection have been completed and two manuscripts are being prepared for publication. A comparison test using MR vaccine is planned.

GVAP linked actions: Ie; IIIb; IIIc; IIId.

✤ Assessment of using Oral Fluid Samples to Estimate Measles Population Immunity, China

Objective and impact: To evaluate the feasibility of using oral fluid samples (OFS) for estimating measles population immunity and identify host and specimen factors (e.g., cigarette smoking, time since last meal) associated with test performance. OFS testing has many logistical advantages over serum testing, including eliminating the need for a needle blood draw. This study will assess whether, and under which circumstances, OFS could replace traditional serosurveys for estimating measles immunity; this information could have significant impact for measles and other vaccine-preventable disease control programs.

Status and outcomes: Enrollment began in early 2014.

GVAP linked actions: Id; IIe.

- **Measles Virus Isolation and Characterization using Filter Paper and Throat Sponges, Democratic Republic of Congo**

  Objective and impact: To evaluate the ability of dried filter paper cards and throat sponges for sample collection to test for measles virus, including genotype, from suspected measles cases. As countries progress towards measles elimination, identifying circulating measles is critical to document the interruption of endemic transmission and identify the source of imported cases. This study will assess whether the use of alternative specimen collection methods is viable in a developing country setting for detecting and characterizing measles virus.

  Status and outcomes: Specimen collection in the field began early 2014.

  GVAP linked actions: Ic; IIe.

- **Comparison of Dried Blood Spots, Oral Fluid, and Sera for Detecting Polio Immunity in Adults, Mozambique**

  Objective and impact: To compare the ability of dried blood spots (DBS), oral fluid, and serum samples to detect neutralizing antibodies to polio virus types 1, 2, and 3 in healthy adult blood donors. This study will evaluate the use of more easily collected specimens to monitor poliovirus immunity in a resource-poor setting.

  Status and outcomes: Approval by the Mozambique ethical review is pending.

  GVAP linked actions: Ic; Id; IIe.

- **Comparison of Sera and DBS for Detecting Polio Immunity in Adults, Malawi**

  Objective and impact: To compare the ability of DBS and serum samples to detect neutralizing antibodies to polio virus types 1, 2, and 3 in healthy adult blood donors. This study will evaluate the use of DBS specimens to monitor poliovirus immunity in a resource-poor setting and with the Mozambique results, provide information on potential test variability by laboratory and setting.

  Status and outcomes: Field specimen collection has been completed; laboratory specimen testing is pending.

  GVAP linked actions: Ic; Id; IIe.

Modeling and Economic Studies

Krysta Gerndt, CDC, with Namibia Ministry of Health medical staff reviewing clinical records in an emergency measles isolation ward, Opuwo District Hospital. Photo by James Goodson (CDC, Atlanta).

✤ Using Integrated Analytic Models to Evaluate Polio Eradication Endgame Strategies

Objective and impact: Several critical issues affect the ability to reach the goal of polio eradication, including 1) understanding transmission and outbreak dynamics, factors that could hasten the interruption of wild polio circulation (e.g., expanded age groups targeted for vaccination), 2) evaluating the consequences of transitioning from OPV to IPV, 3) forecasting vaccine stockpile needs, and 4) characterizing optimal strategies for outbreak response at different phases of the polio endgame. Results of these analyses will provide critical information to guide policy makers and Global Polio Eradication Initiative partners in formulating strategies for the polio endgame.

Polio finger mark, India. Photo by Susan Y. Chu (CDC, Atlanta).

Status and outcomes: This collaboration, which is continuing, has produced numerous publications and presentations at key decision-making and technical expert meetings. Publications include:

- Individual-based modeling of potential poliovirus transmission in connected religious communities in North America with low uptake of vaccination (in press)
- Economic analysis of the global polio eradication initiative. *Vaccine* (29) 2 (2010), pp. 334–343
- Trends in the risk of U.S. polio outbreaks and poliovirus vaccine availability for response. *Public Health Reports* 2012; 127 (1):23–37.
- Preeradication national vaccine policy options for poliovirus infection and disease control. *Risk Analysis.* 2013; 33(4):516–543.
- Expert review on poliovirus immunity and transmission. *Risk Analysis*. 2013; 33(4): 544–605.

"This work has been fundamental to so much of what's happened in the polio eradication program over the last few years, and it has helped to support many of our decisions over the last decade and to bring the world much, much closer to one where future generations will never know the terror of this disease."

- Dr. Bruce Aylward, World Health Organization

- Review and assessment of poliovirus immunity and transmission: Synthesis of knowledge gaps and identification of research needs. *Risk Analysis.* 2013; 33(4):606–646.
- Modeling population immunity to support efforts to end the transmission of live polioviruses. *Risk Analysis*. 2013; 33(4):647–663.
- Oral poliovirus vaccine evolution and insights relevant to modeling the risks of circulating vaccine-derived polioviruses. *Risk Analysis*. 2013; 33(4):680–702.
- Characterizing poliovirus transmission and evolution: Insights from modeling experiences with wild and vaccine-related polioviruses. *Risk Analysis.* 2013; 33(4): 703–749.

GVAP linked actions: Ia; Ie; IIb; IId.

- **Effects of Adult Susceptibility on Measles Transmission Dynamics in the Elimination Era**

Objective and impact: To generate dynamic models that examine the role of susceptible persons in various age groups in propagating measles transmission. The decrease in global measles incidence has shifted measles epidemiology with a greater proportion of cases in young adults. This study will assess the role of young adults, who either lack natural or vaccine-derived immunity, in maintaining measles transmission despite high population immunity in children. This information will be critical for designing appropriate vaccine policy for outbreak and control strategies in the final phases of measles elimination.

Status and outcomes: This collaboration, which is continuing, has provided preliminary findings based on modeling results and manuscripts are in preparation.

GVAP linked actions: Ia; Ie; IIb; IId.

- **Predicting the Cost-effectiveness and Hepatitis B Surface Antigen Prevalence with Different Immunization Strategies, China**

Objective and impact: To evaluate the cost effectiveness and the trend in hepatitis B surface antigen (HBsAg) prevalence associated with various hepatitis B immunization strategies targeted at young adults in China. The current strategy of timely birth dose and universal infant vaccination has dramatically reduced the prevalence of chronic hepatitis B infection in children under 5 years of age from 8% pre-vaccine to currently <1%. There is now considerable interest in China to determine whether additional vaccination efforts targeting adults could effectively interrupt ongoing strategy. This project will use decision trees and modeling to provide information on whether these additional efforts will be programmatically feasible and have public health impact.

Status and outcomes: Analyses are being conducted and a manuscript will be prepared for presentation to the Chinese health officials and policy makers and for publication.

GAVP linked actions: Ia; Ib; Id; IIb.

- **Economic Costs and Benefits of Rubella and Congenital Rubella Syndrome Eradication Pursued in Conjunction with Measles Eradication**

  Objective and impact: To estimate the costs and benefits of rubella and CRS eradication from societal and health sector perspectives when pursued in conjunction with measles eradication. This modeling analysis will provide critical information on the global burden of CRS and the economic feasibility of rubella/CRS eradication, which will contribute to the evidence-based decisions on rubella vaccination policy and programs.

  Status and outcomes: The study is completed and findings were presented to the WHO SAGE evaluating the eradication investment cases for measles and rubella and have been published.

  - Enabling implementation of the Global Vaccine Action Plan: developing investment cases to achieve targets for measles and rubella prevention. *Vaccine.* 2013 Apr 18; 31 Suppl 2:B149–56.

  GVAP linked actions: Ia; Ie; IIb; IId.

- **Determining Appropriate Age Groups for Vaccination to Achieve 2015 and 2020 Measles and Rubella Global Disease Mortality Reduction and Elimination Goals**

  Objective and impact: To characterize the dynamics and cost-effectiveness of different strategies for achieving and maintaining measles and rubella elimination. The current strategy for measles mortality reduction and elimination has not been completely effective in stopping measles transmission in all countries and some countries are reporting increasing cases of measles in adolescents and adults. This analysis will characterize different strategies (e.g., targeted age groups, campaign frequency) required for different situations (e.g., current routine coverage, population density) to help guide future measles immunization programs. For rubella, more than 50 countries will introduce rubella-containing vaccine (RCV) by 2018. This analysis will provide information on the dynamics of introducing RCV into a country that has not yet introduced RCV and the costs and speed of different strategies, which may encourage more rapid adoption of RCV.

  Younger spectators gain courage from watching older children getting their measles and rubella shot in Dolakha District, Nepal. Photo by Umid Sharapov (CDC, Atlanta).

  Status and outcomes: Preliminary results were presented to the WHO SAGE working group and several manuscripts are planned for presenting final results.

  GVAP linked actions: Ia; Ie; IIb; IId.

- **Estimating the Economic Burden of Measles and Rubella Outbreak and Response Activities, Romania**

  Objective and impact: To provide estimates of the economic burden of measles and rubella outbreaks from investigation and response activities in Romania. Romania experienced large-scale measles and rubella outbreaks during 2011–2012, resulting in more than 6,200 reported measles and more than 24,000 rubella cases reported to the WHO. Most studies on the costs of measles and rubella have been in high-income countries, yet the majority of outbreaks occur in low- and middle-income countries. These data will be used by the Romania MOH for decisions affecting their routine immunization program, which can be used as an example of cost-savings when improvements are made in the routine immunization infrastructure in a middle-income country.

  Status and outcomes: Data have been collected in the field and preliminary findings have been reported to the Romanian MOH. A manuscript will be prepared for publication.

  GVAP linked actions: Ia; Ic; IIb.

- **Estimating the Economic Burden of Measles Outbreak and Response Activities, Indonesia**

  Objective and impact: To provide estimates of the economic burden of measles outbreaks from investigation and response activities in Indonesia. The financial and economic costs of a measles outbreak in a developing country are unknown. These data will be used by the Indonesian MOH for decisions affecting their routine immunization program, which can be used as an example of cost-savings when improvements are made in the routine immunization infrastructure of a developing country.

  Status and outcomes: Research in-country partnerships are being established and the study will begin in 2014.

  GVAP linked actions: Ia; Ic; IIb.

Partnerships

This research program has been a success in large part because of the commitment of our international collaborators. Effective global research requires the expertise and insight of those with the greatest understanding of the advantages and challenges in each setting. Because of our in-country partners, the findings from these projects will have the greatest translation and impact.

Outskirts of Kathmandu, Nepal, August 2013. Coverage serosurvey funded by WHO and implemented by a research group in Nepal. CDC-Atlanta and WHO took the lead in developing protocols and data collection tools, training study staff, and analyzing results. Photo by Umid Sharapov (CDC, Atlanta).

✤ Countries and Partners Involved with VPDEEB Research Projects by Funding Year

2011

Countries: Bulgaria, Cambodia, China, Namibia, Nepal, Nigeria, Tajikistan

Partners: WHO; UNICEF; Institute of Medicine at Tribhuvan University; Nepal MOH; Nigerian National Primary Health Care Development Agency; Nigerian Ministry of Agriculture; Namibia MOH and Social Services; Tajikistan MOH; Kid Risk Inc.; Cambodia MOH; CDC Global AIDS Program (GAP), Cambodia office; Center for Infectious Disease Dynamics at Pennsylvania State University (Matt Ferrari); China Center for Disease Control (China CDC); China MOH; Bulgaria MOH; Bulgaria Institute of Public Health; Health Protection Agency for Infections (UK); CDC Division of Viral Diseases (DVD); and CDC Division of Foodborne, Waterborne, and Environmental Diseases (DFWED).

2012

Countries: Bangladesh, Cambodia, China, Democratic Republic of Congo, Indonesia, Laos, Malawi, Mozambique

Partners: WHO; UNICEF; International Centre for Diarrheal Diseases Research, Bangladesh (ICDDR,B); China CDC; China MOH; China Center for Health Education; CDC Beijing office; National Institute of Infectious Diseases Tokyo; Indonesian MOH; Cambodia MOH; National Institute for Public Health, Cambodia; University of Health Sciences, Cambodia; CDC Division of Parasitic Diseases; CDC DVD; University of Maryland; Laos MOH; DRC MOH; RDC Compétence; Mozambique MOH; CDC Mozambique Country Office; CDC GAP; Malawi MOH; CDC Malawi Country Office; Georgia Institute of Technology; Sanofi-Pasteur; and NanoPass Technologies.

2013

Countries: Bangladesh, China, Democratic Republic of Congo, Indonesia, Romania

Partners: CDC DVD; ICDDR,B; Bangladesh MOH; Kid Risk, Inc.; China CDC; Peking University; Georgia Institute of Technology; Romania MOH; Indonesia MOH; CDC DVD; CDC Division of Viral Hepatitis; and CDC DFWED.

Appendix

FIGURE: GVAP Summary of Recommended Actions for Strategic Objective 6

Country, Regional, and Global Research and Development Innovations Maximize the Benefits of Immunization

I. Expand capabilities and increase engagement with end-users

a. Engage with end-users to prioritize vaccines and innovations according to perceived demand and added value.

b. Establish platforms for exchange of information on immunization research and consensus building.

c. Build more capacity and human resources in low- and middle-income countries to conduct research and development and operational research.

d. Increase networking among research centers for efficient building of partnerships among the institutions of high-, middle- and low-income countries.

e. Promote collaboration between traditional research disciplines and scientists from disciplines not previously engaged in vaccine research.

II. Improve program efficiencies and increase coverage and impact

a. Research the use of more effective information through modern communication technologies.

b. Conduct representative epidemiological, immunological, social and operational studies and investigations of vaccine impact to guide health economics analysis.

c. Perform operational research on improved delivery approaches for life-course immunization, and vaccination in humanitarian emergencies, so-called fragile States and countries in and emerging from conflict.

d. Perform research on interference effects and optimum delivery schedules.

e. Perform research to develop improved diagnostic tools for conducting surveillance in low-income countries.

III. Accelerate development, licensing and uptake of vaccines

a. Promote greater access to technology, expertise and intellectual property for adjuvants and their formulation into vaccines.

b. Develop non-syringe delivery mechanisms and vaccine packaging that best suit the needs and constraints of national programmes.

c. Develop thermostable rotavirus and measles vaccines.

d. Develop new bioprocessing and manufacturing technologies.

e. Develop a global, regulatory science research agenda.

f. Adopt best practices in portfolio and partnership management for research and development.

IV. Enable the development of new vaccines

a. Research on the fundamentals of innate and adaptive immune responses, particularly in humans.

b. Research on immunological and molecular characteristics of microbes.

c. Improve understanding of the extent and causes of variation in pathogens and human population responses to vaccines.